Practitioner's Docket No. 49668 (281)

PATENT

TRANSMITTAL LETTER TO THE U.S. DESIGNATED OFFICE (DO/US)-- ENTRY INTO THE U.S. NATIONAL STAGE UNDER CHAPTER I

PCT/JP98/04499	06 October 1998	08 October 1997
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED

RAPIDLY SOLUBLE FILM PREPARATION
TITLE OF INVENTION

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APPLICANT(S)

Box PCT
Assistant Commissioner for Patents
Washington D.C. 20231
ATTENTION: DO/US

NOTE: The completion of those fling requirements that can be made at a time later than 20 months from the priority date results from the Commissioner exercising his judgment under the authority granted under 35 U.S.C. § 371(d). The filing receipt will show the actual date of receipt of the last item completing the entry into the national phase. See 37 C.F.R. § 1.491, which states: "An international application enters the national stage when the applicant has filed the documents and fees required by 35 U.S.C. § 371(c) within the periods set forth in § 1.494 and § 1.495."

WARNING: *Where the items are those that can be submitted to complete the entry of the international application into the national phase subsequent to 20 months from the priority date, the application is still considered to be in the international stage. And if mailing procedures are utilized to obtain a date the express mail procedure of 37 C.F.R. § 1.10 must be used (because international application papers are not covered by an ordinary certificate of mailing. 37 C.F.R. § 1.8(2)(xi)).*

WARNING: *Documents and fees must be clearly identified as a submission to enter the national stage under 35 U.S.C. § 371, otherwise the submission win be considered as being made under 35 U.S.C. § 111. 37 C.F.R. § 1.494(f).*

CERTIFICATION UNDER 37 C.F.R. § 1.10*
*(Express Mail label number is **mandatory.**)*
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I hereby certify that this paper, along with any document referred to, is being deposited with the United States Postal Service on this date April 6, 2000, in an envelope as "Express Mail Post Office to Addressee," mailing Label Number **EL054596762US**, addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

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WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R § 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.*

WARNING:* *Each paper or fee filed by "Express Mail" **must have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. § 1.10(b).*
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WARNING: *Failure to pay the national fee within 20 months from the priority date will result in the abandonment of the application. The time for payment of the basic fee is not extendable. M.P.E.P. § 1893.01(a)(1), 6th ed., rev. 3.*

1. Applicant herewith submits to the United States Designated Office (DO/US) the following items under 35 U.S.C. 371:

a. [X] This express request to immediately begin national examination procedures (35 U.S.C. § 371(f)).

b. [X] The U.S. National Fee (35 U.S.C. § 371(c)(1)) and
[X] other fees (37 C.F.R. § 1.492), as indicated below:

2. Fees

CLAIMS FEE	**(1) FOR**	**(2) NUMBER FILED**	**(3) NUMBER EXTRA**	**(4) RATE**	**(5) CALCULATIONS**
*	**TOTAL CLAIMS**	**13--20**	**0**	**x$ 18.00=**	**$0**
	INDEPENDENT CLAIMS	**1--3**	**0**	**x$ 78.00=**	**$0**
	MULTIPLE DEPENDENT CLAIMS(S) (if applicable) + $260.00				**$260.00**
BASIC FEE**	**The international search fee, as set forth in § 1.445(a)(2) to be paid to the US PTO acting as an international Searching Authority:** **[ ] has been paid (37 CFR 1.492(a)(2))..... $760.00** **[ ] has not been paid (37 CFR 1.492(a)(3))..... $970.00** **[X] where a search report on the international application has been prepared by the European Patent Office or the Japanese Patent Office (37 CFR 1.492(a)(5)) $840.00**				**$840.00**
	Total of above Calculation				**= $1,100.00**
SMALL ENTITY	**Reduction by ½ for filing by small entity, if applicable. Affidavit must be filed also. (note 37 CFR 1.9, 1.27, 1.28)**				**-**
	Subtota				**$1,100.00**
	Total National Fe				**$1,100.00**
	Fee for recording the enclosed assignment document $40.00 (37 CFR 1.21(h)). (See Item 10 below). See attached "ASSIGNMENT COVER SHEET (37 CFR 3.34)".				**$40.00**
TOTAL	**Total Fees enclose**				**$1,140.00**

***WARNING:* *"To avoid abandonment of the application, the applicant shall furnish to the United States Patent and Trademark Office not later than the expiration of 20 months from the priority date; *** (2) the basic national fee (see § 1.492(a)). The 20-month time limit may not be extended." 37 C.F.R. § 1.494(b).*

i [X] A check in the amount of $ 1,140.00 to cover the above fees is enclosed.
ii. [ ] Please charge Account No. _____ in the amount of $ _____.
A duplicate copy of this sheet is enclosed.

WARNING: *If the translations of the international application and/or oath or declaration have not been submitted by the applicant within twenty (20) months from the priority date, the applicant will be so notified and given a period of time within which to file the translation and/or oath or declaration in order to prevent abandonment. The payment of the surcharge set forth in § 1.492(e) is required as a condition for accepting the oath or declaration later than twenty (20) months after the priority date. The payment of the processing fee set forth in § 1.492(f) is required for acceptance of an English translation later than twenty (20) months after the priority date. Failure to comply with these requirements will result in abandonment of the application. The provisions of § 1.136 will apply. 37 C.F.R. § 1.494(c).*

3. A copy of the International application as filed (35 U.S.C. § 371(c)(2)):
a. [X] is transmitted herewith.
b. [ ] is not required, as the application was filed with the United States Receiving Office.
c. [ ] has been transmitted
i. [ ] by the International Bureau. Date of mailing of the application Prom form PCT/IB/308): _____.
ii. [ ] by applicant on _____.
Date

NOTE: *Section 1.494(b) was amended to require that the basic national fee and a copy of the international application must be filed with the Office by 20 months from the priority date to avoid abandonment. "The International Bureau nominally provides the copy of the international application to the Office in accordance with PCT Article 20. At the same time, the International Bureau notifies the applicant of the communication to the Office. In accordance with PCT Rule 47.1, that notice shall be accepted by all designated offices as conclusive evidence that the communication has duly taken place. Thus, if the applicant desires to enter the national stage and applicant has received notice from the International Bureau, applicant need only pay the basic national fee by 20 months from the priority date." [This can now be paid subsequently with a surcharge.] Notice of Jan. 7, 1993, 1147 O.G. 29 to 40, at 35.*

4. A translation of the International application into the English language (35 U.S.C. § 371(c)(2)):
a. [X] is transmitted herewith.
b. [ ] is not required as the application was filed in English.
c. [ ] was previously transmitted by applicant on _____.
Date

5. [X] Amendments to the claims of the International application under PCT Article 19 (35 U.S.C. § 371(c)(3)):

NOTE: *The Notice of January 7, 1993 indicates that 37 C.F.R. § 1.494(d) was "amended to clarify the existing practice that PCT Article 19 Amendments must be submitted by 20 months from the priority date, which time may not be extended." This Notice further advises: "Of course, the failure to do so does not result in loss of the subject matter of PCT Article 19 amendments. The applicant may submit that subject matter in a preliminary amendment filed under Section 1.121. In many cases, filing an amendment under Section 1.121 is preferable since grammatical or idiomatic errors may be corrected." 1147 O.G. 29-40, at 35. See item 11(c) below. See also 37 C.F.R. § 1.494(d).*
a. [ ] are transmitted herewith.
b. [ ] have been transmitted

i. [ ] by the International Bureau. Date of mailing of the amendment (from form PCT/IB/308): _____.

ii. [ ] by applicant on _____.
Date

c. [X] have not been transmitted, as

i. [ ] no notification has been received that the International Search Authority has received the Search Copy.

ii [ ] the Search Copy was received by the International Searching Authority, but the Search Report has not yet been issued. Date of receipt of Search Copy prom form PCT/ISA/202):_____.

iii. [X] applicant chose not to make amendments under PCT Article 19. Date of mailing of Search Report (from form PCT/ISA/210): 01 January 1999

iv. [ ] the time limit for the submission of amendments has not yet expired. The amendments, or a statement that amendments have not been made, will be transmitted before the expiration of the time limit under PCT Rule 46.1.

6. [X] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. § 371(c)(3)):

a. [ ] is transmitted herewith.

b. [ ] is not required as the amendments were made in the English language.

c. [X] has not been transmitted for reasons indicated at point 5(c) above.

7. [X] An oath or declaration of the inventor including power of attorney (35 U.S.C. § 371(c)(4)) complying with 35 U.S.C. § 115

a. [ ] was previously submitted by applicant on _____
Date

b. [X] is submitted herewith, and such oath or declaration

i. [X] is attached to the application.

ii. [ ] identifies the application and any amendments under PCT Article 19 that were transmitted as stated in points 3(b) or (c) and 5(b); and states that they were reviewed by the inventor, as required by 37 C.F.R. § 1.70.

iii. [ ] will follow.

II. Other document(s) or information included:

8. [X] An international Search Report or Declaration under PCT Article 17(2)(a):

a. [X] is transmitted herewith.

b. [ ] has been transmitted by the International Bureau. Date of mailing from form PCT/IB/308): _____.

c. [ ] is not required, as the application was searched by the United States International Searching Authority.

d. [ ] will be transmitted promptly upon request.

e. [ ] has been submitted by applicant on _____.
Date

f. [ ] is not transmitted, as the international search has not yet issued.

9. [X] An Information Disclosure Statement under 37 C.F.R. §§ 1.97 and 1.98:
   a. [ ] is transmitted herewith.
      Also transmitted herewith is (are)
      [ ] Form PTO-1449 (PTO/SB/08A and 08B)
      [ ] Copies of citations listed
   b. [X] will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. § 371(c).
   c. [ ] was previously submitted by applicant on _____.
      Date

10. [X] An assignment document is transmitted herewith for recording. A separate
    [ ] "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or
    [X] FORM PTO—1595 is also attached.
    [X] Please mail the recorded assignment document to:
       i. [X] the person whose signature and address appears below.
       ii. [ ] the following:

11. [X] Additional documents
    a. [X] Copy of request (PCT/RO/101)
    b. [X] International Publication No. WO 99/59948
       i. [X] Specification, claims and drawing
       ii. [ ] Front page only
    c. [ ] Preliminary amendment (37 C.F.R. § 1.121)
    d. [X] Other:
       Copy of Form PCT/IB/301
       Copy of Form PCT/IB/304
       Copy of Form PCT/IB/308
       Copy of Form PCT/IPEA/408 (and 1 reference cited)
       Copy of Form PCT/IPEA/416

12. [X] The above checked items are being transmitted
    a. [ ] before the 18th month publication.
    b. [X] after publication and the article 20 communication, but before 20 months from the priority date.
    c. [ ] after 20 months (revival).

NOTE: Petition to revive (37 C.F.R. § 1.137(a) or (b)) is necessary if 35 U.S.C. § 371 requirements are submitted after 20 months.

13. [ ] Certain requirements under 35 U.S.C. § 371 were previously submitted by the applicant on _____ namely:
    Date

AUTHORIZATION TO CHARGE ADDITIONAL FEES

WARNING: *Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges if extra claims are authorized.*

NOTE: *"A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under § 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in § 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 C.F.R. § 1.136(a)(3).*

NOTE: *"Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 C.F.R. § 1.26(a).*

[X] The Commissioner is hereby authorized to charge the following additional fees that may be required by this paper and during the entire pendency of this application to Account No. 04-1105 .

[X] 37 C.F.R. § 1.492(a)(1), (2), (3), and (4) (filing fees)

WARNING: *Because failure to pay the national fee within 20 months without extension (37 C.F.R. § 1.494(b)(2)), results in abandonment of the application, it would be best to always check the above box.*

[X] 37 C.F.R. § 1.492(b), (c), and (d) (presentation of extra claims)

NOTE: *Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment, prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 C.F.R. § 1.16(d)), it might be best not to authorize the PTO to charge additional claim fees, except possibly when dealing with amendments after final action.*

[X] 37 C.F.R. § 1.17 (application processing fees)
[ ] 37 C.F.R. § 1.17(a)(1)-(5)(extension fees pursuant to § 1.136(a).

[ ] 37 C.F.R. § 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. § 1.311(b)).

NOTE: *Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 C.F.R. § 1.311(b).*

NOTE: *37 C.F.R. § 1.28(b) requires "Notification of any change in status resulting in loss of entitlement to small entity status must be filed in the application . . . prior to paying or at the time of paying . . . issue fee...." From the wording of 37 C.F.R. § 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.*

[ ] 37 C.F.R. § 1.492(e) and (f) (surcharge fees for filing the declaration and/or filing an English translation of an International Application later than 20 months after the priority date.

SIGNATURE OF PRACTITIONER

Reg. No. 33,860

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DESCRIPTION

RAPIDLY SOLUBLE FILM PREPARATION

TECHNICAL FIELD

The present invention relates to a film preparation (film-shaped drug) rapidly soluble in the oral cavity, and more particularly to a rapidly soluble film preparation for oral administration containing a saccharide in a base, for the purpose of allowing a drug to be mainly absorbed into the digestive organs by rapidly dissolving the drug in the oral cavity.

BACKGROUND ART

At present, as the drugs orally administered, naked tablets, coated tablets, capsules, powders, granules, pills and aqueous drugs (solutions) have been put on the market. Then, the preparations for oral application include buccal tablets and mucosa-adhesive film preparations. However, these are ones in which the drugs are allowed to be absorbed through the mucous membranes in the oral cavity, or ones for the purpose of treatment of diseases in the oral cavity, and are not ones for the purpose of usual drug absorption into the digestive tracts. Almost all of these are contrived to continuously release the drugs, and no rapidly soluble ones have been known.

Drugs commercially available as merely film-shaped, tape-shaped or sheet-shaped ones, not adhesive to the mucous membranes in the oral cavity, are not found. However, as seen

from documents (patents), (A) a sheet-shaped administration formation such as medicine, confectionery, other food, a cosmetic or an article similar thereto orally administered or incorporated, which comprises 20 to 60% by weight of at least one film forming agent, 2 to 40% by weight of at least one gel forming agent, 0.1 to 35% by weight of at least one active substance (drug) and further less than 40% by weight of at least one inactive filler, and rapidly decomposes in water (Toku-Kai-Hei (Japanese Unexamined Patent Publication) 7-100186), and (B) a tape having a tensile strength of at least 200 psi (about 14 kg/cm^2), a drug/mm^3 of 0.01 to 2 mg and an optimum solubility to the drug, and having a composition comprising about 10 to 40% by weight of a physiologically acceptable thermoplastic polymer, about 15 to 50% by weight of a saccharide, about 5 to 40% by weight of a physiologically acceptable plasticizer and about 0 to 20% by weight of a physiologically acceptable lubricant (Toku-Kai-Hei 5-220203) are known. Further, (C) a sheet-shaped solid pharmaceutical composition characterized in that a solution or a suspension containing a substance having physiologically active action by the existence thereof in slight amounts is printed on, spread on, sprayed on, or injected into a pharmaceutically acceptable sheet-shaped carrier (Toku-Kai-Hei 5-124954) is also known.

However, in the above-mentioned invention (A), it is described that "it is an object of this invention to provide an administration formation rapidly decomposing in water and individually formulated in a sheet form" (the publication, page

8, right column, [0028]), but what contrivance causes the formation to rapidly decompose is not described at all. Although a drug is obtained in Example 2, merely "the drug decomposes in the mouth" (the publication, page 10, left column, [0064]) is only described, and details such as for the time for decomposition of the drug decomposes are not clear. In this Example 2, the temperature is elevated to 80°C in preparation, so that a considerable period of time is taken for cooling after mixing and the like, which causes a disadvantage in the manufacturing process. Further, in the above-mentioned invention (B), sorbitol (lubricant) is used as one useful to enhance speeds of disintegration and dissolution of the tape. However, it is described that "for further assisting dissolution, a disintegrating agent, for example, cross caramelose Na type A, can be used in an amount of not exceeding about 10% by weight", and this is considered because the use of only sorbitol sometimes results in an insufficient disintegration rate. Furthermore, in this invention, the drug tape is mounted on a dispenser, so that it is necessary to have a definite tensile strength. Control for the tensile strength is therefore required in production, which is disadvantageous to efficiency in actual production. Still further, in the above-mentioned invention (C), the substance showing physiologically activity by the existence thereof in slight amounts (a drug: for example, 0.02 mg per unit, in the case of mestranol) is utilized. The drug is effectively used in such slight amounts, so that the solution or suspension of the drug

is printed on, spread on, sprayed on, or injected into the sheet-shaped carrier. However, this is time-consuming and not economical. Then, with respect to one shown in Fig. 1 of the published specification, not only slights are provided, but also punching is performed with a punch, resulting in complication of the process.

An object of the invention is to economically provide a film preparation having no disadvantages observed in the above-mentioned known film preparations, that is to say, rapidly dissolved, simply produced and economically obtained.

DISCLOSURE OF THE INVENTION

The present inventors have variously studied for obtaining a film preparation having sufficient rapid solubility by a simple process by the addition of one ingredient. As a result, the present inventors have discovered that the use of a drug, an edible polymer and a monosaccharide, a sugar alcohol or an oligosaccharide in combination can solve the above-mentioned problems, thus completing the present invention.

That is to say, the present invention relates to (1) a rapidly soluble film preparation mainly comprising a drug, an edible polymer and a saccharide, (2) the rapidly soluble film preparation described in (1), in which the content of the drug is from 0.01 to 50% by weight, that of the edible polymer is from 20 to 90% by weight, and that of the saccharide is from 1 to 50% by weight, (3) the rapidly soluble film preparation described in (1), in which the drug is a compound enhanced in

internal absorption by the conversion to a solid solution, (4) the rapidly soluble film preparation described in (3), in which the compound enhanced in internal absorption by the conversion to the solid solution is nilvadipine, (5) the rapidly soluble film preparation described in (1), in which the edible polymer is one selected from the group consisting of synthetic polymers, cellulose derivatives and natural polymers, (6) the rapidly soluble film preparation described in (1) or (5), in which the edible polymer is at least one selected from the group consisting of poly(vinylpyrrolidone), hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxyethyl cellulose and ethyl cellulose, (7) the rapidly soluble film preparation described in (1) or (2), in which the saccharide is one selected from the group consisting of monosaccharides, sugar alcohols and oligosaccharides, (8) the rapidly soluble film preparation described in (7), in which the oligosaccharide is starch syrup, (9) the rapidly soluble film preparation described in (8), in which the starch syrup is reducing maltose starch syrup, (10) the rapidly soluble film preparation described in (1), in which the drug is a compound which can be enhanced in internal absorption by the conversion to a solid solution, the edible polymer is one or more of poly(vinyl-pyrrolidone) and hydroxypropyl cellulose, and an additional edible polymer, and the saccharide is starch syrup, and (11) the rapidly soluble film preparation described in (10), in which the compound enhanced in internal absorption by the conversion to the solid solution is nilvadipine, the additional

edible polymer is hydroxypropyl cellulose, and the starch syrup is reducing maltose starch syrup.

As apparent from the above, the film preparation of the invention is characterized in that it is rapidly dissolved in the oral cavity and can be taken without water, as a dosage form substitutive for a tablet.

The invention is described in detail below. The invention is the rapidly soluble film preparation in which the drug is allowed to be contained in a film base comprising the edible polymer such as poly (vinylpyrrolidone), hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxyethyl cellulose or ethyl cellulose, and the monosaccharide, the sugar alcohol or the oligosaccharide, and which is easily produced and has no conventional disadvantages as described above.

BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 is a graph showing the elution rate of a rapidly soluble film preparation of the invention.

BEST MODE FOR CARRYING OUT THE INVENTION

The saccharides used in the invention include sugar alcohols such as erythritol, pentitol and hexitol, monosaccharides (aldose and ketose) and oligosaccharides. Specifically, the sugar alcohols include xylitol, mannitol, D-sorbitol and reducing maltose starch syrup, the monosaccharides include glucose and fructose, the oligosaccharides

include maltose, lactose and sucrose, and the monosaccharide-oligosaccharides include starch syrup. Reducing maltose starch syrup is particularly preferred. The compounding amount of the saccharides in the film preparation of the present invention is from 1 to 50% by weight, and preferably from 5 to 50% by weight. Less than 1% results in the insufficient rate of dissolution, whereas exceeding 50% raises a problem with regard to the shape retaining property of products, although the rate of dissolution is increased. Many of the saccharides have sweet tastes, and this is advantageous for the film preparations soluble in the mouth. Further, many of them also act as plasticizers, like starch syrup. Accordingly, when they are used, it is not necessary to especially use plasticizers. Of course, the plasticizers may be used as so desired. When sorbitol is used as the saccharide, sorbitol sometimes deposits as crystallites on film surfaces. However, the drug effect and the others are not affected at all.

There is no particular limitation on the edible polymer which is a component of the film base of the invention, as long as it has film forming ability and is edible. The edible polymers include synthetic polymers, for example, poly(vinylpyrrolidone) (hereinafter described as "PVP"), carboxyvinyl polymers (hereinafter described as "CVPs"), polyvinyl alcohol (hereinafter described as "PVA") and the like, cellulose derivatives, such as hydroxypropyl methyl cellulose (hereinafter described as "HPMC"), hydroxypropyl cellulose

(hereinafter described as "HPC"), hydroxyethyl cellulose (hereinafter described as "HEC"), methyl cellulose (hereinafter described as "MC"), ethyl cellulose (hereinafter described as "EC") and the like, and polymers obtained from natural products, for example, sodium alginate, dextran, casein, pullulan and the like. Particularly preferred are PVP and HPC. These substances can be used either alone or as a combination of two or more of them.

The total compounding amount of the edible polymers in the film preparation is from 20 to 90% by weight, and preferably from 25 to 80% by weight in all.

For the rapidly soluble film preparations of the invention, aromatics, coloring matter, preservatives, antioxidants, stabilizing agents, surfactants, plasticizers and the like may be properly used as components of the film bases, as so desired, in addition to the above-mentioned substances.

There is no particular limitation on the drugs used in the invention, as long as they can be orally administered. Specific examples thereof include calcium antagonists such as nilvadipine and nicardipine, β2-stimulants such as procaterol hydrochloride and fenoterol hydrobromide, oral antidiabetic drugs such as glibenclamide, somniferous drugs such as brotizolam and triazolam, β-blockers such as arotinolol hydrochloride and carteolol hydrochloride, therapeutic drugs for the coronary vessels such as nicorandil, anesthetics such as dibucaine hydrochloride, nonsteroidal anti-inflammatory drugs such as diclofenac sodium and indomethacin, and sedatives

such as diphenhydramine hydrochloride and scopolamine hydrobromide.

As the drugs used in the invention, ones having no bitter tastes are suitable. However, even ones having bitter tastes can be used in the invention by masking such as microcapsulation. The compounding amount of the drugs in the film preparation is usually from 1 to 50% by weight, although it varies depending on the properties of the drugs.

The rapidly soluble film preparations of the invention are produced, for example, by the following method.

Specified amounts of the edible polymer, saccharide and drug are dissolved in a solvent in which these substances are soluble, for example, ethanol, and the resulting solution is spread on a liner film and dried to obtain a film. The film is cut to a desired size, and hermetically packaged if necessary to provide a product. The dissolution of the drug can be accelerated by heating to about 50 to about 60℃ in preparing the solution. Further, when foams are developed in the solution in preparing it, standing overnight or vacuum deaeration is preferably conducted. There is no particular limitation on the solvent used in preparing the solution, as long as it dissolves the respective compounding components. Either a single solvent or a combined solvent may be used. Specifically, the solvents include ethanol, a mixture of ethanol and water, and the like.

In the invention, it has been found that when the specified edible polymers are used, some kinds of drugs are

enhanced in internal absorption thereof. That is to say, for example, when the drug is nilvadipine, the use of poly-(vinylpyrrolidone) and/or hydroxypropyl methyl cellulose as the edible polymer(s) enhances the internal absorption. This is considered to be caused by the formation of a good solid solution by nilvadipine with these polymers. In this case, the film preparation can be produced by the use of only poly-(vinylpyrrolidone) and/or hydroxypropyl methyl cellulose as the edible polymer(s), but an additional edible polymer can provide a better film preparation. For example, in the case of nilvadipine, hydroxypropyl cellulose is suitably used.

Specific examples of the drugs forming the solid solutions with the edible polymers include nifedipine, phenytoin, chloramphenicol, griseofulvin, sulfamethizole and the like, as well as nilvadipine.

EXAMPLES

The invention is described below in detail with reference to examples. These examples are not to be construed as limiting the invention.

Example 1

To a suitable amount of ethanol, 4.0 parts by weight of nilvadipine, 76.0 parts by weight of HPC and 20.0 parts by weight of reducing maltose starch syrup were added and dissolved by stirring. This was spread on a polyester liner film and dried to produce a film having a thickness of about 250 μm. The resulting film was cut to a square, 16 mm each side, thereby obtaining a film preparation rapidly soluble in the oral cavity.

Example 2

To a suitable amount of ethanol, 4.0 parts by weight of nilvadipine, 72.0 parts by weight of HPC, 4.0 parts by weight of PVP and 20.0 parts by weight of reducing maltose starch syrup were added and dissolved by stirring. This was spread on a polyester liner film and dried to produce a film having a thickness of about 250 μm. The resulting film was cut to a square, 16 mm each side, thereby obtaining a film preparation rapidly soluble in the oral cavity.

Examples 3 to 6

According to formulations of Table 1, rapidly soluble film preparations were obtained in the same manner as with Example 2.

Table 1

Name of Component	Examples			
	3	4	5	6
Nilvadipine	4.0	4.0	4.0	4.0
HPC	64.0	56.0	51.0	46.0
PVP	12.0	20.0	20.0	20.0
Reducing Maltose Starch Syrup	20.0	20.0	25.0	30.0
Total	100.0	100.0	100.0	100.0

Example 7

To a suitable amount of ethanol, 4.0 parts by weight of nilvadipine, 72.0 parts by weight of HPC, 4.0 parts by weight of HPMC and 20.0 parts by weight of reducing maltose starch syrup were added and dissolved by stirring. This was spread on a

polyester liner film and dried to produce a film having a thickness of about 250 μm. The resulting film was cut to a square, 16 mm each side, thereby obtaining a film preparation rapidly soluble in the oral cavity.

Examples 8 to 14

According to formulations of Table 2, rapidly soluble film preparations were obtained in the same manner as with Example 7.

Table 2

Name of Component	Examples						
	8	9	10	11	12	13	14
Nilvadipine	4.0	4.0	4.0	4.0	4.0	4.0	4.0
HPC	64.0	56.0	51.0	46.0	56.0	56.0	56.0
HPMC	12.0	20.0	20.0	20.0	-	-	-
MC	-	-	-	-	20.0	-	-
EC	-	-	-	-	-	20.0	-
HEC	-	-	-	-	-	-	20.0
Reducing Maltose Starch Syrup	20.0	20.0	25.0	30.0	20.0	20.0	20.0
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Example 15

To a suitable amount of ethanol, 20.0 parts by weight of nicardipine hydrochloride, 40.0 parts by weight of HPC, 20.0 parts by weight of PVP and 20.0 parts by weight of reducing maltose starch syrup were added and dissolved by stirring. This

was spread on a polyester liner film and dried to produce a film having a thickness of about 250 μm. The resulting film was cut to a square, 16 mm each side, thereby obtaining a film preparation rapidly soluble in the oral cavity.

Examples 16 to 21

According to formulations of Table 3, rapidly soluble film preparations were obtained in the same manner as with Example 15.

Table 3

Name of Component	Examples					
	16	17	18	19	20	21
Fenoterol Hydro-Bromide	5.0	4.0	-	-	-	-
Indomethacin	-	-	2.0	2.0	2.0	2.0
HPC	55.0	56.0	78.0	58.0	78.0	58.0
PVP	20.0	20.0	-	-	-	20.0
Reducing Maltose Starch Syrup	20.0	-	20.0	40.0	-	20.0
D-Sorbitol	-	20.0	-	-	20.0	-
	100.0	100.0	100.0	100.0	100.0	100.0

Examples 22 and 23

According to formulations of Table 4, rapidly soluble film preparations were obtained in the same manner as with Example 7.

Table 4

Name of Component	Examples	
	22	23*
Nilvadipine	4.0	4.0
PVP	76.0	20.0
EC	-	56.0
Reducing Maltose Starch Syrup	20.0	20.0
Total	100.0	100.0

(*Ethanol:purified water = 3:1)

Example 24

To a suitable amount of an ethanol-purified water (2:1) mixture, 4.0 parts by weight of nilvadipine, 6.0 parts by weight of HPMC and 20.0 parts by weight of reducing maltose starch syrup were added and dissolved by stirring. This was spread on a polyester separate film and dried to produce a film having a thickness of about 250 μm. The resulting film was cut to a square, 16 mm each side, thereby obtaining a film preparation rapidly soluble in the oral cavity.

Examples 25 to 28

According to formulations of Table 5, rapidly soluble film preparations were obtained in the same manner as with Example 24.

Table 5

Name of Component	Examples			
	25	26	27	28*
Nilvadipine	4.0	4.0	4.0	4.0
HPC	-	56.0	-	-
PVP	20.0	-	-	-
HPMC	-	20.0	20.0	20.0
MC	56.0	-	56.0	-
EC	-	-	-	56.0
Reducing Maltose Starch Syrup	20.0	20.0	20.0	20.0
Total	100.0	100.0	100.0	100.0

(*Ethanol:purified water = 3:1)

Example 29

To a suitable amount of a mixture of ethanol-purified water (2:1), 4.0 parts by weight of nilvadipine, 38.0 parts by weight of PVP, 38.0 parts by weight of HPMC and 20.0 parts by weight of reducing maltose starch syrup were added and dissolved by stirring. This was spread on a polyester liner film and dried to produce a film having a thickness of about 250 μm. The resulting film was cut to a square, 16 mm each side, thereby obtaining a film preparation rapidly soluble in the oral cavity.

Examples 30 to 32

According to formulations of Table 6, rapidly soluble film preparations were obtained in the same manner as with Example 29.

Table 6

Name of Component	Examples		
	30	31	32*
Nilvadipine	4.0	4.0	4.0
HPC	36.0	-	-
PVP	20.0	20.0	20.0
HPMC	20.0	20.0	20.0
MC	-	36.0	-
EC	-	-	36.0
Reducing Maltose Starch Syrup	20.0	20.0	20.0
Total	100.0	100.0	100.0

(*Ethanol:purified water = 3:1)

Comparative Example 1

To a suitable amount of ethanol, 4.0 parts by weight of nilvadipine, 76.0 parts by weight of HPC and 20.0 parts by weight of PVP were added and dissolved by stirring. This was spread on a polyester liner film and dried to produce a film having a thickness of about 250 μm. The resulting film was cut to a square, 16 mm each side, thereby obtaining a film preparation rapidly soluble in the oral cavity.

Comparative Example 2

To a suitable amount of ethanol, 2.0 parts by weight of indomethacin and 98.0 parts by weight of HPC were added and dissolved by stirring. This was spread on a polyester liner film and dried to produce a film having a thickness of about 250μm. The resulting film was cut to a square, 16 mm each side,

thereby obtaining a film preparation rapidly soluble in the oral cavity.

(Elution Test)

Test Method

In a 100-ml tall beaker, 100 ml of purified water is placed, and stirred (100 rpm) with a stirrer. One piece of sample (16 mm X 16 mm) is placed in a cylindrical stainless steel basket, and put under the water in the beaker. Then, the basket is fixed. After a definite period of time from initiation of the test, 500 μl was sampled, and determined with the HPLC. Results are shown in Fig. 1.

INDUSTRIAL APPLICABILITY

The film preparations of the invention are very easily produced, have high rapid solubility, are extremely high in practical use, and are suitable for using as film preparations for oral administration.

CLAIMS

1. A rapidly soluble film preparation mainly comprising a drug, an edible polymer and a saccharide.

2. The rapidly soluble film preparation according to claim 1, in which the content of the drug is from 0.01 to 50% by weight, that of the edible polymer is from 20 to 90% by weight, and that of the saccharide is from 1 to 50% by weight.

3. The rapidly soluble film preparation according to claim 1, in which the drug is a compound which can be enhanced in internal absorption by the conversion to a solid solution.

4. The rapidly soluble film preparation according to claim 3, in which the compound is nilvadipine.

5. The rapidly soluble film preparation according to claim 1, in which the edible polymer is one selected from the group consisting of synthetic polymers, cellulose derivatives and natural polymers.

6. The rapidly soluble film preparation according to claim 1 or 5, in which the edible polymer is at least one selected from the group consisting of poly(vinylpyrrolidone), hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxyethyl cellulose and ethyl cellulose.

7. The rapidly soluble film preparation according to claim 1 or 2, in which the saccharide is one selected from the group consisting of monosaccharides, sugar alcohols and oligosaccharides.

8. The rapidly soluble film preparation according to claim 7, in which the oligosaccharide is starch syrup.

9. The rapidly soluble film preparation according to claim 8, in which the starch syrup is reducing maltose starch syrup.

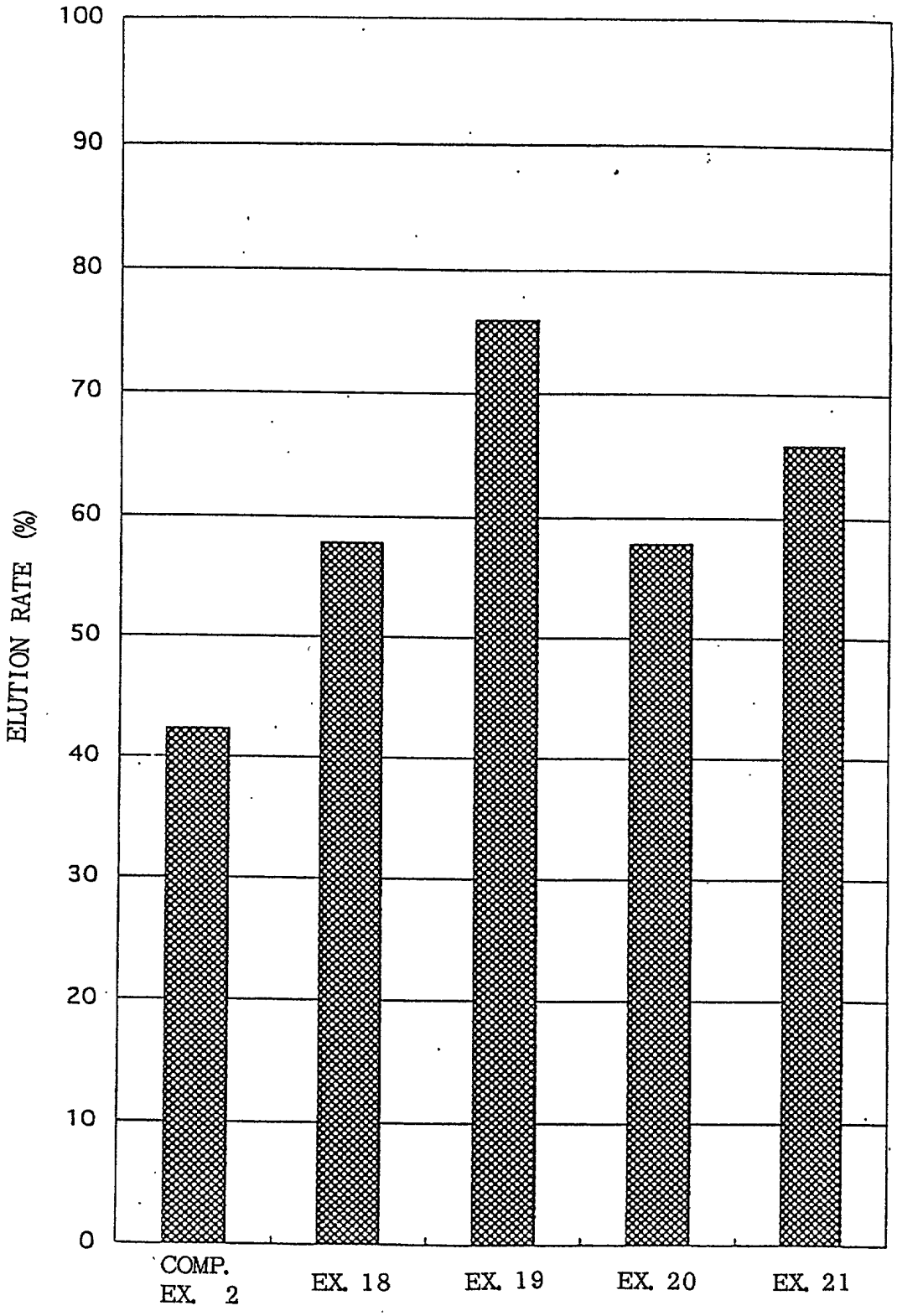
10. The rapidly soluble film preparation according to claim 1, in which the drug is a compound which can be enhanced in internal absorption by the conversion to a solid solution, the edible polymer is one or more of poly(vinylpyrrolidone) and hydroxypropyl cellulose, and an additional edible polymer, and the saccharide is starch syrup,

11. The rapidly soluble film preparation according to claim 10, in which the compound is nilvadipine, the additional edible polymer is hydroxypropyl cellulose, and the starch syrup is reducing maltose starch syrup.

ABSTRACT

Disclosed is a rapidly soluble film preparation mainly comprising a drug, an edible polymer and a saccharide, a manufacturing method of which is simple, and having high elution rate.

FIG. 1



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DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that: My residence, post office address and citizenship are as stated below next to my name. I believe I am the original, first and sole inventor (if only one name is listed at 201) below or an original, first and joint inventor (if plural names are listed at 201-208 below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

RAPIDLY SOLUBLE FILM PREPARATION

which is described and claimed in:

☐ the specification attached hereto.

☐ the specification in U.S. Application Serial Number _____, filed on _____.

☒ the specification in PCT international application Number PCT/JP98/04499, filed on 06.10.98; and was amended on _____.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a). I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

Prior Foreign/PCT Applications and Any Priority Claims Under 35 U.S.C. 119:			
Application No.	**Filing Date**	**Country**	**Priority Claimed Under 35 U.S.C. 119?**
9-275967	October 8, 1997	JAPAN	☒YES ☐NO
			☐YES ☐NO
			☐YES ☐NO
			☐YES ☐NO
			☐YES ☐NO
			☐YES ☐NO
			☐YES ☐NO

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below, and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose material information as defined in 37 CFR §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

Prior U.S. Applications or PCT International Applications Designating the U.S-Benefit Under 35 U.S.C. §120					
U.S. Applications			Status (Check One)		
Application Serial No.	U.S. Filing Date		Patented	Pending	Abandoned
PCT Applications Designating the U.S.					
Application No.	Filing Date	U.S. Serial No. Assigned			

CLAIM FOR BENEFIT OF PRIOR U.S. PROVISIONAL APPLICATION(S)
(35 U.S.C. § 119(e))

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

Applicant	Provisional Application Number	Filing Date

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) with full powers of association, substitution and revocation to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

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